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(74) Agents: KEZER, William, B. et al.; Townsend and  
Townsend and Crew LLP, 8th floor, Two Embarcadero  
Center, San Francisco, CA 94111-3834 (US).

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60/155,318 12 September 1999 (12.09.1999) US

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BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK,  
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IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,  
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,  
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,  
UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent  
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent  
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,  
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant: CELLEGY PHARMACEUTICALS, INC.  
[US/US]; 349 Oyster Point Boulevard, Suite 200, South  
San Francisco, CA 94080 (US).

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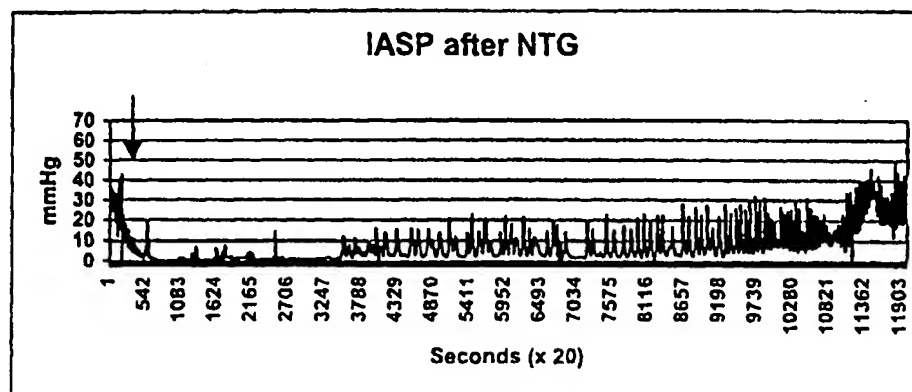
- With international search report.
- Before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments.

(72) Inventors: PARKS, Thomas, P.; 541 Parrott Drive, San  
Mateo, CA 94402 (US). MAK, Vivien; 1185 Newell Road,  
Palo Alto, CA 94303 (US). LEE, Jung-Chung; 1628 Crow  
Court, Sunnyvale, CA 94087 (US). LEE, Charles; 2452  
Medallion Drive, Union City, CA 94587 (US).

(88) Date of publication of the international search report:  
30 November 2000

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(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF ANORECTAL DISORDERS



(57) Abstract: Compositions and methods for the treatment of anorectal disorders are provided in which certain combinations of NO donors, PDE inhibitors, superoxide (O<sub>2</sub><sup>-</sup>) scavengers,  $\beta$ -adrenergic agonists, cAMP-dependent protein kinase activators,  $\alpha_1$ -adrenergic antagonists, L-type Ca<sup>2+</sup> channel blockers, estrogens, ATP-sensitive K<sup>+</sup> channel activators and smooth muscle relaxants are used.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/29459

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/21 A61K31/195 A61K31/34 A61K31/4015  
A61K31/472 A61K31/517 A61K31/522 A61K31/137 A61P43/00  
A61P17/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 19672 A (NITROMED INC.) 14 May 1998 (1998-05-14) page 55, line 3 -page 60, line 25 ---	1-4, 23-26
X	WO 95 32715 A (NEPTUNE PHARMACEUTICAL CORPORATION) 7 December 1995 (1995-12-07) claims 1-36 page 8, line 35 -page 9, line 5 ---	1,3, 23-26
X	DE 41 17 249 A (CASSELLA AG) 3 December 1992 (1992-12-03) claims 1-6 ---	1,3
X	WO 97 27749 A (NITROMED INC.) 7 August 1997 (1997-08-07) claims 3-10,22 ---	1,3
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	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

30 June 2000

Date of mailing of the international search report

27.09.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Siatou, E

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/29459

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 27971 A (M. KAMM ET AL) 2 July 1998 (1998-07-02) page 6, line 25 - line 28 claims 1-12 ---	1-7, 23-26
A	WO 95 06466 A (KOREN LABORATORIES PTY. LTD) 9 March 1995 (1995-03-09) the whole document ---	1-7, 23-26
A	RATTAN S ET AL: "ROLE OF NITRIC OXIDE AS A MEDIATOR OF INTERNAL ANAL SPHINCTER RELAXATION" AMERICAN JOURNAL OF PHYSIOLOGY: GASTROINTESTINAL AND LIVER PHYSIOLOGY,US,AMERICAN PHYSIOLOGICAL SOCIETY, vol. 262, no. 1, PART 01, 1 January 1992 (1992-01-01), pages 107-112, XP002059676 ISSN: 0193-1857 abstract ---	1-7, 23-26
A	GORFINE: "Treatment of benign anal disease with topical nitroglycerin" DISEASES OF THE COLON AND RECTUM,US,J.B. LIPPINCOT CO., PHILADELPHIA, vol. 38, no. 5, 1 May 1995 (1995-05-01), pages 453-457, XP002084601 ISSN: 0012-3706 abstract -----	1-7

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/29459

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 23-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7, 23-26

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-7, 23-26

Treatment of anorectal disorders by using a combination composition of a nitric oxide (NO) donor and a second agent selected from phosphodiesterase inhibitors, superoxide scavengers, beta-adrenergic agonists, cAMP-dependent protein kinase activators, alpha-adrenergic antagonists, estrogens, ATP-sensitive potassium channel activators and smooth muscle relaxants.

2. Claims: 8-10 and 27-28

Treatment of anorectal disorders by a composition comprising a phosphodiesterase inhibitor

3. Claims: 11-14, 29-30

Treatment of anorectal disorders by using a composition containing a beta-adrenergic agonist

4. Claims: 15-16, 31-32

Treatment of anorectal disorders by using a composition containing an ATP-sensitive potassium channel activator

5. Claims: 17-19

Treatment of anorectal disorders by using a composition containing an alpha-1-adrenergic antagonist

6. Claims: 20-22, 33

Treatment of anorectal disorders by using a composition containing a cyclic nucleotide-dependent protein kinase activator

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/29459

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9819672 A	14-05-1998	US 5874437 A AU 722480 B AU 5196298 A EP 0941086 A US 5958926 A	23-02-1999 03-08-2000 29-05-1998 15-09-1999 28-09-1999
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LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,  
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(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,  
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant: **CELLEGY PHARMACEUTICALS, INC.**  
[US/US]; 349 Oyster Point Boulevard, Suite 200, South  
San Francisco, CA 94080 (US).

**Published:**

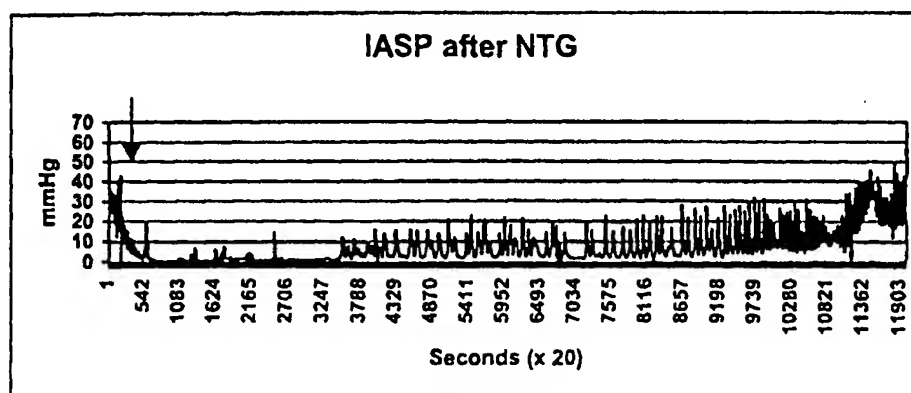
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(72) Inventors: **PARKS, Thomas, P.**; 541 Parrott Drive, San  
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Court, Sunnyvale, CA 94087 (US). **LEE, Charles**; 2452  
Medallion Drive, Union City, CA 94587 (US).

(88) Date of publication of the international search report:  
30 November 2000

[Continued on next page]

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International Application No

PCT/US 99/29459

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A61K31/472 A61K31/517 A61K31/522 A61K31/137 A61P43/00  
A61P17/04

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 98 19672 A (NITROMED INC.) 14 May 1998 (1998-05-14) page 55, line 3 -page 60, line 25 ---	1-4, 23-26
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X	WO 97 27749 A (NITROMED INC.) 7 August 1997 (1997-08-07) claims 3-10,22 --- -/-	1,3



Further documents are listed in the continuation of box C.



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\*A\* document defining the general state of the art which is not considered to be of particular relevance

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\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

30 June 2000

Date of mailing of the international search report

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3018

Authorized officer

Siatou, E

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/29459

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	GORFINE: "Treatment of benign anal disease with topical nitroglycerin" DISEASES OF THE COLON AND RECTUM,US,J.B. LIPPINCOT CO., PHILADELPHIA, vol. 38, no. 5, 1 May 1995 (1995-05-01), pages 453-457, XP002084601 ISSN: 0012-3706 abstract -----	1-7

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Although claims 23-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
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1-7, 23-26

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-7, 23-26

Treatment of anorectal disorders by using a combination composition of a nitric oxide (NO) donor and a second agent selected from phosphodiesterase inhibitors, superoxide scavengers, beta-adrenergic agonists, cAMP-dependent protein kinase activators, alpha-1-adrenergic antagonists, estrogens, ATP-sensitive potassium channel activators and smooth muscle relaxants.

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4. Claims: 15-16, 31-32

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Treatment of anorectal disorders by using a composition containing an alpha-1-adrenergic antagonist

6. Claims: 20-22, 33

Treatment of anorectal disorders by using a composition containing a cyclic nucleotide-dependent protein kinase activator

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/29459

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9819672 A	14-05-1998	US 5874437 A AU 722480 B AU 5196298 A EP 0941086 A US 5958926 A	23-02-1999 03-08-2000 29-05-1998 15-09-1999 28-09-1999
WO 9532715 A	07-12-1995	US 5504117 A AT 196082 T AU 2282395 A CA 2168247 A CN 1131392 A DE 719145 T EP 0719145 A ES 2092460 T GR 96300077 T JP 9504037 T US 5693676 A	02-04-1996 15-09-2000 21-12-1995 07-12-1995 18-09-1996 13-02-1997 03-07-1996 01-12-1996 31-01-1997 22-04-1997 02-12-1997
DE 4117249 A	03-12-1992	AT 195870 T AU 1877992 A CA 2110275 A WO 9221346 A EP 0586621 A US 5492911 A	15-09-2000 08-01-1993 10-12-1992 10-12-1992 16-03-1994 20-02-1996
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WO 9827971 A	02-07-1998	AU 5331598 A EP 0946155 A	17-07-1998 06-10-1999
WO 9506466 A	09-03-1995	AU 708694 B AU 7454594 A ZA 9500511 A	12-08-1999 22-03-1995 11-03-1996